Long-term oral budesonide treatment and risk of osteoporotic fractures in patients with microscopic colitis

Reilev, Mette; Hallas, Jesper; Thomsen Ernst, Martin; Nielsen, Gunnar Lauge; Bonderup, Ole K

Published in:
Alimentary Pharmacology & Therapeutics

DOI (link to publication from Publisher):
10.1111/apt.15648

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

DR METTE REILEV (Orcid ID : 0000-0003-1241-4385)

DR OLE K BONDERUP (Orcid ID : 0000-0003-3199-3474)

Article type : Original Scientific Paper

Long-term oral budesonide treatment and risk of osteoporotic fractures in patients with Microscopic Colitis

Running title: Budesonide treatment and risk of fractures

Target journal: Alimentary Pharmacology and Therapeutics

Authors:

Mette Reilev MD PhD [1]

Jesper Hallas MD DMSc[1]

Martin Thomsen Ernst[1,2]

Gunnar Lauge Nielsen MD[3,4]

Ole K Bonderup MD, PhD[5]

Affiliations

[1] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense University Hospital, Denmark

[2] OPEN - Open Patient data Explorative Network, Department of Clinical Research, University of Southern Denmark, Denmark

[3] Department of Internal Medicine, Aalborg University Hospital, Aalborg, Denmark

[4] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[5] Diagnostic Centre, Regional Hospital Silkeborg, and University Research Clinic for Innovative Patient Pathways, Aarhus University, Denmark

Corresponding author:

Ole K Bonderup

Diagnostic Centre

Silkeborg Regional Hospital

Falkevej 1

8600 Silkeborg

Denmark

E-mail: olebonde@rm.dk

Word count: Abstract: 246; Text: 2510

Abstract

Background

Due to a substantial first-pass metabolism of oral budesonide, systemic bioavailability is low compared to other oral corticosteroids, thereby possibly avoiding adverse effects of systemic corticosteroid use.

Aims

To determine whether use of oral budesonide is associated with osteoporotic fractures in patients with microscopic colitis.

Methods

Applying data from the Danish nationwide health registries, we conducted a case-control study nested within a cohort of patients with microscopic colitis from 2004 to 2012. We estimated odds ratios (ORs) for the association between budesonide use and osteoporotic fractures (hip-, wrist and spinal fractures).

Results

We identified 417 cases with a first occurrence of an osteoporotic fracture. Eighty-six percent were women and the median age was 78 years. The OR for the overall association between ever-use of budesonide and any osteoporotic fractures did not reach statistical significance (OR 1.13, CI: 0.88-1.47). The highest risk was observed for spinal fractures (OR 1.98, CI: 0.94-4.17), where a dose-response association seemed to exist, followed by hip-, and wrist fractures (OR 1.17 (CI: 0.79-1.73) and OR 0.99 (CI: 0.66-1.47), respectively). We generally found modestly increased ORs across subgroups at suspected high or low risk of fractures (1.00-2.49). No overall dose-response association was evident (OR for doubling of cumulative dose 0.93 (CI: 0.84-1.03).

Conclusion

No overall association between use of oral budesonide and osteoporotic fractures was demonstrated among individuals with microscopic colitis. There seemed to be an isolated adverse effect of budesonide on the risk of spinal fractures, which appears to be dose-related.

Key words

Oral budesonide, osteoporotic fractures, spinal fractures, microscopic colitis

Introduction

The controlled-release formulations of oral budesonide are proven both effective and well-tolerated in patients with ileocecal Crohn´s disease[1,2] and have been a breakthrough in the treatment of microscopic colitis (MC).[3,4] Unlike most other oral corticosteroids, budesonide has a substantial first-pass metabolism. Thereby, it exerts an immunosuppressant effect in the gut wall and is subsequently metabolized in the liver, thus resulting in quite a low systemic bioavailability, about 10%[1] compared to more than 80% for prednisolone.[5] This ingenious leveraging of first-pass metabolism has enabled us to use budesonide for maintenance treatment of MC without undue toxicity.[3,4]

However, adverse effects related to long-term use of corticosteroids are of concern. Oral corticosteroids in general are known to increase the risk of osteoporotic fractures through a reduction in bone formations and osteocyte apoptosis.[6] The risk of fractures may vary across different corticosteroids, which is emphasized by studies indicating an increased risk among users of prednisolone[7] whereas a similar association is debatable for budesonide.[8] Despite a reduced systemic

availability of budesonide, this may still be enough to increase the risk of osteoporosis particularly among long-term users.

Oral budesonide is exclusively used for patients with MC, inflammatory bowel diseases and autoimmune hepatitis. The latter two patients groups are often marked by substantial systemic inflammation, malnutrition and underweight,[9] all potent risk factors for osteoporosis.[10,11] This may potentially confound the observed association between long-term use of budesonide and osteoporotic fractures towards an apparently increased risk. Intending to avoid such confounding, we therefore aimed to determine whether use of budesonide is associated with an increased risk of osteoporotic fractures in a population restricted to patients with MC.

Material and Methods

Using Danish nationwide health registries, we conducted a case-control study nested within a population of patients with MC, thereby assessing the association between use of budesonide and osteoporotic fractures.

Data sources

We retrieved data from four nationwide, population-based registries: The Danish Pathology Registry, The National Prescription Registry, The Danish National Patient Registry, and The Danish Civil Registration System. Data were linked by a unique Civil Person Registry number, which is provided to all Danish citizens.[12]

The Danish Pathology Registry contains data on pathological findings from all Danish pathology Departments since 1997. Diagnoses are coded according to the modification of the Systematized Nomenclature of Medicine (SNOMED).[13]

The National Prescription Registry records data on all redeemed prescription drugs by Danish citizens at outpatient pharmacies since 1995 and onward[14]. Among others, prescription data include the date of dispensing and the substance. Drugs are categorized according to the Anatomical Therapeutic Chemical (ATC) code, developed by the WHO for purposes of drug use statistics.[15]

The Danish National Patient Registry records data on all hospital admissions since 1977 and contacts to outpatient clinics since 1995. Among others, data includes information on date of admission and the discharge diagnoses coded by the International Classification of Disease 10th version (ICD-10).[16]

The Danish Civil Person Registry covers every Danish citizen and records data on vital status (date of birth and death) and migrations to and from Denmark.[12]

Source population

Cases and controls above 18 years of age were sampled from the nationwide Danish Pathology Registry entailing 9,234 persons with a diagnosis of MC, either collagenous colitis (n = 5380) or lymphocytic colitis (n = 3854) from January 2004 to December 2012. All MC diagnoses were histologically verified. We excluded subjects with a previous diagnosis of Crohn´s disease, ulcerative colitis or autoimmune hepatitis (**Figure 1**). Subjects were eligible as cases or controls from the date of their histological MC diagnosis and were eligible for being sampled as cases or controls until the first occurrence of an outcome, emigration, death or end of the study period, whichever event came first.

Cases and controls

Cases were subjects from the source population who within the study period had their first occurrence of a fracture likely caused by osteoporosis, i.e., hip fractures (ICD10 S72), wrist fractures (ICD10 S525) and spinal compression fractures, both thoracic and lumbar (ICD10 S320, S220). Controls were patients with microscopic colitis without fractures.

Using a risk set sampling technique, controls were sampled in a ratio of 1:3 from the source population. Thus, for each case we identified three randomly selected controls who matched the case by age, sex and type of MC. Controls were assigned an index date identical to the outcome date of the corresponding case. Each subject could be sampled as a control more than once. Cases were eligible as controls until their outcome date. Thereby, the estimated odds ratio is an unbiased estimate of the incidence rate ratio that would have emerged from a cohort study in the source population, albeit with a much more efficient estimation.[17]

As some of the very old cases had less than three eligible controls, the final case:control ratio deviated slightly from 1:3.

Exposure

Main exposure was ever-use of oral budesonide received before the index date. To be able to investigate dose-response associations, we further categorized use of budesonide into mutually exclusive categories: less than 100 defined daily doses (DDD), 100 - 199 DDD, 200 - 499 DDD and 500 DDD or more. This categorization was based on explorative analyses of drug utilization in the

source population. 1 DDD of budesonide corresponds to a daily dose of 9 mg, which is the recommended dose of budesonide in the treatment of MC.

Analysis

The analysis conformed to a conventional matched case-control design. We estimated odds ratios (ORs) using conditional logistic regression, while controlling for a set of preselected confounders i.e., forced variables (use of nicotine substitutes, malnutrition, kidney failure, chronic obstructive pulmonary disease, and alcohol abuse) as well as data driven confounders. A data driven confounder was selected if it changed the OR of the budesonide-fracture association by more than 2% when added to a crude analysis.[18] Only use of antidepressants fulfilled this criterion. Crude and adjusted ORs were presented with 95% confidence intervals. Of note, confounding by age, sex and calendar time was handled by the risk set sampling and conditional analysis.

In the main analysis, we estimated the association between ever-use of budesonide and any osteoporotic fractures. This analysis was repeated for single sub-outcomes separately i.e., hip fractures, wrist fractures and spinal fractures. In addition, we investigated a dose-response association by estimating ORs within preselected categories of accumulated use of budesonide (in DDD) and by performing a formal dose-response analysis using the base 2 logarithm of the accumulated amount of budesonide as main independent variable. In this particular dose-response analysis, all unexposed subjects were excluded.

We performed additional supplementary and sensitivity analyses. First, to uncover potential subgroups at particularly high or low risk of osteoporotic fractures, we investigated the association between ever-use of budesonide and any osteoporotic fractures when stratifying the population by sex, age and type of MC (lymphocytic colitis or collagenous colitis). Secondly, to avoid the influence of potential recovery of bone mass related to past budesonide use, we performed a dose-response analysis in which we restricted the population to individuals who had been exposed to budesonide within the previous two years. Thirdly, acknowledging that some induction time is needed to develop osteoporotic fractures based on budesonide treatment, we introduced a 6-month lag-time before the index date in a sensitivity analysis. Finally, to reduce confounding by use of other corticosteroids, we restricted the population to subjects without previous treatment with other systemic corticosteroids than budesonide. In all analyses, never-use of budesonide was used as the reference.

The analyses were performed using Stata version 15.1 The project was approved by the Danish Data Protection Board (J.nr. 2014 – 41 – 3214). According to Danish law, review by an ethics committee is not required for purely registry-based studies.[19]

Results

In a study population of individuals with MC, we identified 417 cases with a first occurrence of a fracture likely caused by osteoporosis. They were matched to 1240 controls. The majority were women (86%) and the median age was 78 years. In general, the distribution of comorbid diseases was uniform among cases and controls. More cases had been exposed to budesonide (35% vs. 30% among controls) and antidepressants (43% vs. 28% among controls) (**Table 1**).

After adjustment for confounding, a modestly increased OR was observed for the overall association between ever-use of budesonide and any osteoporotic fractures (OR 1.13, CI: 0.88-1.47), however without reaching statistical significance (**Table 2**). No dose-response association was evident for osteoporotic fractures in general. Accordingly, the OR for doubling of cumulative dose of budesonide was 0.93 (CI: 0.84-1.03) (**Table 2**). Stratification by type of fracture revealed the highest risk of spinal fractures (OR 1.98, CI: 0.94-4.17), followed by hip-, and wrist fractures (OR 1.17 (CI: 0.79-1.73) and OR 0.99 (CI: 0.66-1.47), respectively) (**Table 3**). A dose-response association seemed to appear for individuals having spinal fractures. As such, the OR for spinal fractures was 1.04 for individuals with the lowest intake of budesonide increasing to OR 3.34 for individuals with an accumulated use of 500+ DDD, whereas the OR for doubling of cumulative dose was 1.11 (CI: 1.01-1.22). For wrist- and hip fractures, the risk remained unchanged irrespective of cumulative dose of budesonide (**Table 3**).

To address potential differences across subgroups, we stratified the population by sex, age and type of MC. Apart from a modestly increased OR in individuals <65 years (OR 2.49), we did not find any subgroups with particularly strong or weak associations (**Table 4**).

Restricting the population to never-users of other systemic corticosteroids than budesonide, recent users of budesonide and introducing a 6-month lag-time prior to the index date did not change the conclusions (**E-table 1, E-table 2 and E-table 3**).

Discussion

In this nationwide study we observed a small increase in the OR of osteoporotic fractures, not reaching statistically significance, in patients with MC treated with oral budesonide. Specifying by fracture type revealed a weak association for spinal fractures, where a dose-response association also seemed to exist. For wrist and hip fractures no such association was observed. Except from a modestly increased risk among individuals <65 years, we did not find any subgroups with particularly strong or weak associations.

The main strength of this study is the restriction to patients with a diagnosis of MC. Due to the limited systemic inflammatory impact of MC with no clinical signs of malabsorption this approach ensures a uniform study population with a minimal risk of confounding by systemic inflammation, malnutrition and underweight otherwise possibly overestimating the results. Moreover, detailed information of co-morbidity and drug exposure made it possible to adjust for such confounding.

Another strength is the nationwide, registry-based approach. The highly valid recording of diagnoses in the Danish Pathology Registry and in the Danish Patient Registry ensures a valid definition of both study population and outcome. Further, the Danish Prescription Registry permits a detailed assessment of budesonide exposure, since budesonide always requires a prescription and is not available over-the-counter. Our data represents drugs that have actually been purchased at the pharmacies, mitigating the influence of primary non-adherence.[20] Of note, the applied Danish Health Registries have nationwide coverage of all Danish citizens irrespective of socio-economic status, thereby reducing the risk of selection bias. In addition, the validity of fracture diagnoses is generally high.[21]

The registry-based approach did not provide complete information on a range of life style factors, including smoking history, alcohol consumption, BMI and physical activity, potentially confounding the observed association. Such confounding was handled by adjusting for proxies, although some residual confounding cannot be ruled out. However, since it appears unlikely that life style factors would affect the decision to use budesonide, the resulting misclassification of potential confounders would affect the results minimally.

Though orally administered systemic steroids are associated with a risk of fractures, the risk seems to vary by type of corticosteroids. Vestergaard et al. found an OR of 0.93 among individuals with an average daily consumption of oral prednisolone of less than 6.67 mg/day increasing to an OR of 1.55 among those using more than 13.3 mg prednisolone per day.[8] Low dose treatment with budesonide

(around 3 mg/day) was not associated with an increased risk of fracture.[8] Other studies indicate that an increased risk of fractures could be the effect of long-term treatment with oral budesonide on bone mineral density. One clinical study demonstrated a decreased bone density in patients with Crohn's disease,[22] using a mean dose of budesonide of 8.5 mg/day (range, 6-9 mg/day) for 2 years. In another study on patients with primary biliary cirrhosis, oral budesonide (6 mg/d for three years) was associated with a decrease in bone mass density.[23] However, relatively small study populations and a possible effect of pre-treatment conditions have limited the conclusions.

In a study of 50 patients with MC treated with budesonide, no significant differences in bone mineral density were observed when compared to a healthy control group.[24] However, the markers of bone formation P1NP (Pro-N-terminal peptide procollagen type 1) were lower in patients with MC than in controls, suggesting an osteoblast dysfunction due to the systemic effect of budesonide or to the disease itself.

From a pharmacological viewpoint, an increased fracture risk among users of budesonide is not entirely implausible. Though the systemic bioavailability of budesonide is low, a conventional daily oral dose of 9 mg budesonide is equivalent of a daily oral intake of 4-5 mg of prednisolone[8] – a steroid dose that cannot be considered innocuous.[25] The small but non-significant increase in the overall risk of osteoporotic fractures demonstrated in our study could be in agreement with this notion. The lack of dose-response effect for fractures overall is, however, difficult to explain.

There seems to exist an association with use of budesonide for spinal fractures. This is further consolidated by the existence of a dose-response association for this specific fracture type though not statistically significant within preselected categories of accumulated use of budesonide. This dose-response analysis has the drawback that subjects who belong to the same category are treated similarly in the analysis, whether they have high or low use within that category, thereby reducing statistical power. This problem is handled by performing a regression directly on the cumulative dose, thus preserving the statistical power and in this study, proving a statistically significant dose-response association. Since spinal fractures are usually spontaneous and notoriously related to osteoporosis, while traumas more often are involved in hip and wrist fractures, an isolated effect on spinal fractures is biologically plausible.[26] Moreover, the increased susceptibility to glucocorticoid of trabecular bone predominating in the vertebral bone adds to the observed differences across fracture types.[27]

Our analyses on ongoing users suggest that the absence of an association for hip- and wrist fractures is not explained by recovery between treatment episodes among intermittent users of budesonide. A

substantial part of the explanation could therefore be in the traumatic component for hip and wrist fractures. Calcium supplement and D-vitamins are sold over the counter, and we thus cannot account for all anti-osteoporotic prophylactic measures used by our subjects. It is conceivable that such measures are channeled to those at highest risk.

There is good evidence that anti-osteoporotic treatment, such as bisphosphonates, is effective against steroid induced osteoporosis and fractures.[28] Whether it applies to our scenario as well has not been tested, to our knowledge. For most clinicians, however, it would seem reasonable to extrapolate from studies on other corticosteroids.

This study cannot confirm an association between use of budesonide and osteoporotic fractures in general. There seems to be an isolated adverse effect of budesonide on the risk of spinal fractures which appears to be dose-related. This is plausible from a pharmacological perspective. Whether it warrants measures to prevent osteoporotic spinal fractures remains to be established.

Acknowledgements

None

Authorship statement

Ole Bonderup has received speaker fees from Tillotts and Dr Falk Pharma, is a member of an advisory board for Tillotts and has received grants from Tillotts.

The study is supported by an unrestricted grant from Tillotts.

Jesper Hallas, Martin Thomsen Ernst, Gunnar Lauge Nielsen, and Mette Reilev declare no further conflicts of interest in relation to this study.

References

1. Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. *Clin Pharmacokinet*. 2004;43(12):803-821. doi:10.2165/00003088-200443120-00003

2. Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2008;(3):CD000296. doi:10.1002/14651858.CD000296.pub3

3. Kafil TS, Nguyen TM, Patton PH, MacDonald JK, Chande N, McDonald JW. Interventions for treating collagenous colitis. *Cochrane Database Syst Rev*. 2017;11:CD003575. doi:10.1002/14651858.CD003575.pub6

4. Chande N, Al Yatama N, Bhanji T, Nguyen TM, McDonald JW, MacDonald JK. Interventions for treating lymphocytic colitis. *Cochrane Database Syst Rev*. 2017;7:CD006096. doi:10.1002/14651858.CD006096.pub4

5. Brattsand R. Overview of Newer Glucocorticosteroids Preparations for Inflammatory Bowel Disease. *Canadian Journal of Gastroenterology*. 1990(vol. 4, 7):pp.407-414.

6. van Staa TP. The pathogenesis, epidemiology and management of glucocorticoid-induced osteoporosis. *Calcif Tissue Int*. 2006;79(3):129-137. doi:10.1007/s00223-006-0019-1

7. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with systemic and topical corticosteroids. *J Intern Med*. 2005;257(4):374-384. doi:10.1111/j.1365-2796.2005.01467.x

8. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with different types of oral corticosteroids and effect of termination of corticosteroids on the risk of fractures. *Calcif Tissue Int*. 2008;82(4):249-257. doi:10.1007/s00223-008-9124-7

9. Ferguson A, Sedgwick DM. Juvenile onset inflammatory bowel disease: height and body mass index in adult life. *BMJ*. 1994;308(6939):1259-1263.

10. De Laet C, Kanis JA, Odén A, et al. Body mass index as a predictor of fracture risk: a meta-analysis. *Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA*. 2005;16(11):1330-1338. doi:10.1007/s00198-005-1863-y

11. Azzopardi N, Ellul P. Risk factors for osteoporosis in Crohn's disease: infliximab, corticosteroids, body mass index, and age of onset. *Inflamm Bowel Dis*. 2013;19(6):1173-1178. doi:10.1097/MIB.0b013e31828075a7

12. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29(8):541-549. doi:10.1007/s10654-014-9930-3

13. Bjerregaard B, Larsen OB. The Danish Pathology Register. *Scand J Public Health*. 2011;39(7 Suppl):72-74. doi:10.1177/1403494810393563

14. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H, Sørensen HT, Hallas J, Schmidt M. Data Resource Profile: The Danish National Prescription Registry. *Int J Epidemiol*. 2017;46(3):798-798f. doi:10.1093/ije/dyw213

15. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2017. 2017.

16. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490. doi:10.2147/CLEP.S91125

17. Rothman KJ. *Epidemiology, an Introductio*. 2nd edition. page 90-92: Oxford Press

18. Rothman KJ. *Epidemiology, An Introduction*. 2nd edition. page 223: Oxford Press

19. Thygesen LC, Daasnes C, Thaulow I, Bronnum-Hansen H. Introduction to Danish (nationwide) registers on health and social issues: Structure, access, legislation, and archiving. *Scand J Public Health*. 2011;39(7 Suppl):12-16. doi:10.1177/1403494811399956

20. Beardon PH, McGilchrist MM, McKendrick AD, McDevitt DG, MacDonald TM. Primary non-compliance with prescribed medication in primary care. *BMJ*. 1993;307(6908):846-848. doi:10.1136/bmj.307.6908.846

21. Hundrup YA, Høidrup S, Obel EB, Rasmussen NK. The validity of self-reported fractures among Danish female nurses: comparison with fractures registered in the Danish National Hospital Register. *Scand J Public Health*. 2004;32(2):136-143.

22. Cino M, Greenberg GR. Bone mineral density in Crohn's disease: a longitudinal study of budesonide, prednisone, and nonsteroid therapy. *Am J Gastroenterol.* 2002;97(4):915-921. doi:10.1111/j.1572-0241.2002.05609.x

23. Rautiainen H, Färkkilä M, Neuvonen M, et al. Pharmacokinetics and bone effects of budesonide in primary biliary cirrhosis. *Aliment Pharmacol Ther.* 2006;24(11-12):1545-1552. doi:10.1111/j.1365-2036.2006.03155.x

24. Wildt S, Munck LK, Becker S, Brockstedt H, Bonderup OK, Hitz MF. Risk of osteoporosis in microscopic colitis. *Postgrad Med.* 2018;130(3):348-354. doi:10.1080/00325481.2018.1441579

25. van Staa TP, Leufkens HGM, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. *Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA.* 2002;13(10):777-787. doi:10.1007/s001980200108

26. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet Lond Engl.* 2019;393(10169):364-376. doi:10.1016/S0140-6736(18)32112-3

27. van Staa TP, Leufkens HGM, Apenheim L, Zhang B, Cooper C. Use of corticosteroids and the risk of fractures. *J **Bone** Miner Res.* 2000;15(6):993-1000. doi:10.1359/jbmr.2000.15.6.993

28. Allen CS, Yeung JH, Vandermeer B, Homik J. Bisphosphonates for steroid-induced osteoporosis. *Cochrane Database Syst Rev.* 2016 Oct 5;10:CD001347. doi:10.1002/14651858.CD001347.pub2

Tables

Table 1. Characteristics of enrolled cases and controls on the event date**.**

	Cases N = 417	Controls N = 1240
Demographics		
Female (%)	357 (86%)	1065 (86%)
Age, median (IQR)	78 (68 - 85)	78 (68 - 84)
Collagenous Colitis	267 (64%)	795 (64%)

Lymphocytic Colitis	150 (36%)	445 (36%)
Comorbidity		
Upper gastrointestinal diseases		
Gastro-oesophageal reflux disease	41 (10%)	73 (6%)
Gastroduodenal ulcer	55 (13%)	126 (10%)
Gastroduodenitis	39 (9%)	108 (9%)
Celiac disease	9 (2%)	23 (2%)
Liver diseases		
Alcoholic liver diseases	6 (1%)	11 (1%)
Cirrhosis of liver	5 (1%)	n<5
Cancer		
Gastrointestinal cancer (total)	18 (4%)	53 (4%)
Colon cancer	12 (3%)	30 (2%)
Lung cancer	5 (1%)	8 (1%)
Endocrine diseases		
Hypothyroidism	23 (6%)	51 (4%)
Hyperthyroidism	20 (5%)	48 (4%)
Obesity	17 (4%)	36 (3%)
Type 1 Diabetes mellitus	21 (5%)	45 (4%)
Type 2 Diabetes mellitus	38 (9%)	87 (7%)
Lung diseases		
Asthma	154 (37%)	436 (35%)
COPD	108 (26%)	305 (25%)
Vascular diseases	69 (17%)	193 (16%)
Hypertension		
Ishaemic heart diseases	14 (3%)	42 (3%)
Stroke	56 (13%)	118 (10%)
Rheumatoid diseases		
Reumatoid arthritis	16 (4%)	52 (4%)
Arthropatia	n<5	n<5
Artritis	7 (2%)	40 (3%)
Arthrosis	106 (25%)	296 (24%)
Spondylarthritis	n<5	n<5

Drug exposure		
Corticosteroids	173 (41%)	454 (37%)
Steroid inhalants for COPD	5 (1%)	31 (3%)
Topical rectal	n<5	n<5
Prednisolone (oral)	32 (8%)	91 (7%)
Budesonide (oral)	144 (35%)	374 (30%)
PPI	176 (42%)	432 (35%)
Anticoagulants	19 (5%)	78 (6%)
Platelet inhibitors	167 (40%)	474 (38%)
Thiazides	58 (14%)	211 (17%)
Estrogenes	40 (10%)	149 (12%)
Lipid lowering drugs	116 (28%)	394 (32%)
Thyroid hormones	38 (9%)	114 (9%)
Anti-thyroids	12 (3%)	28 (2%)
NSAID´s	97 (23%)	231 (19%)
Calcium/D-vitamin	16 (4%)	36 (3%)
Bisphosphonates	72 (17%)	161 (13%)
Antidepressants	178 (43%)	350 (28%)
Drug used in nicotine dependence	n<5	n<5
Drug used in alcohol dependence	n<5	n<5
Inhalants for COPD	5 (1%)	31 (3%)

PPI: proton pump inhibitor; NSAID: non-steroid anti-inflammatory drug; COPD: Chronic obstructive pulmonary disease

Table 2. Relative risk of any osteoporotic fracture among ever-users of budesonide. Never use of budesonide was used as the reference value.

	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude odds ratio 95% CI	Adjusted *) odds ratio 95% CI
No use	0 / 108	0 / 370	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
Ever-use	309 / 108	870 / 370	1.22 (0.95 - 1.58)	1.13 (0.88 - 1.47)
Dose response				
0-99 DDD	149 / 108	388 / 370	1.41 (1.02 - 1.95)	1.37 (0.98 - 1.90)
100-199 DDD	70 / 108	236 / 370	0.80 (0.53 - 1.23)	0.71 (0.45 - 1.12)

200-499 DDD	59 / 108	179 / 370	1.35 (0.85 - 2.14)	1.29 (0.80 - 2.09)
500+ DDD	31 / 108	67 / 370	1.91 (0.94 - 3.87)	1.63 (0.77 - 3.43)
Log(cumulative DDD)	NA	NA	0.96 (0.88 - 1.06)	0.93 (0.84 - 1.03)

**) Adjusted for* use of nicotine substitutes, malnutrition, kidney failure, COPD, alcohol abuse and antidepressant use.

CI: 95% confidence interval

DDD: Defined daily dose

Ref: Reference value

Log: base 2 logarithm

Table 3. Dose-response association between budesonide use and types of osteoporotic fractures. Never use of budesonide was used as reference value.

	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude odds ratio 95% CI	Adjusted *) odds ratio 95% CI
Spinal fracture				
No use	0 / 13	0 / 60	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
Ever use	46 / 13	114 / 60	2.05 (1.00 - 4.20)	1.98 (0.94 - 4.17)
0-99 DDD	17 / 13	54 / 60	1.12 (0.40 - 3.10)	1.04 (0.36 - 3.04)
100-199 DDD	10 / 13	30 / 60	2.59 (0.62 - 10.92)	2.47 (0.51 - 12.01)
200-499 DDD	12 / 13	18 / 60	3.09 (0.94 - 10.14)	2.81 (0.65 - 12.22)
500+ DDD	7 / 13	12 / 60	2.74 (0.62 - 12.04)	3.34 (0.55 - 20.35)
Log(cumulative DDD)	NA	NA	1.11 (1.01 - 1.22)	1.11 (1.01 - 1.22)
Wrist fracture				
No use	0 / 45	0 / 134	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
Ever use	118 / 45	350 / 134	1.00 (0.68 - 1.49)	0.99 (0.66 - 1.47)
0-99 DDD	61 / 45	156 / 134	1.48 (0.88 - 2.46)	1.61 (0.95 - 2.73)
100-199 DDD	26 / 45	99 / 134	0.46 (0.23 - 0.92)	0.34 (0.15 - 0.78)
200-499 DDD	24 / 45	72 / 134	1.30 (0.64 - 2.63)	1.36 (0.64 - 2.91)
500+ DDD	7 / 45	23 / 134	0.57 (0.14 - 2.25)	0.31 (0.06 - 1.59)
Log(cumulative	NA	NA	0.99 (0.94 - 1.04)	0.99 (0.93 - 1.04)

DDD)				
Hip fracture				
No use	0 / 50	0 / 176	1.00 (1.00 - 1.00)	1.00 (1.00 - 1.00)
Ever use	145 / 50	406 / 176	1.25 (0.87 - 1.81)	1.17 (0.79 - 1.73)
0-99 DDD	71 / 50	178 / 176	1.43 (0.90 - 2.26)	1.33 (0.82 - 2.18)
100-199 DDD	34 / 50	107 / 176	1.02 (0.56 - 1.87)	1.02 (0.51 - 2.03)
200-499 DDD	23 / 50	89 / 176	0.99 (0.47 - 2.07)	0.81 (0.36 - 1.82)
500+ DDD	17 / 50	32 / 176	3.73 (1.16 - 11.98)	2.97 (0.87 - 10.11)
Log(cumulative DDD)	NA	NA	1.03 (0.98 - 1.08)	1.01 (0.96 - 1.06)

**) Adjusted for* use of nicotine substitutes, malnutrition, kidney failure, COPD, alcohol abuse and antidepressant use.

CI: 95% confidence interval

DDD: Defined daily dose

Ref: Reference value

Log: base 2 logarithm

Table 4. Subgroup analysis of the association between ever-use of budesonide use and osteoporotic fractures.

Subgroup	Cases Exposed/unexposed	Controls Exposed/unexposed	Crude odds ratio 95% CI	Adjusted *) odds ratio 95% CI
Men	42 / 18	107 / 68	1.50 (0.80 - 2.79)	1.14 (0.59 - 2.23)
Women	267 / 90	763 / 302	1.18 (0.89 - 1.55)	1.10 (0.83 - 1.45)
Age <65	55 / 13	138 / 61	2.10 (1.03 - 4.30)	2.49 (1.17 - 5.34)
Age ≥65	254 / 95	732 / 309	1.13 (0.86 - 1.47)	1.04 (0.79 - 1.37)
Type of MC				
LC	103 / 47	298 / 147	1.10 (0.74 - 1.64)	1.00 (0.66 - 1.52)
CC	206 / 61	572 / 223	1.31 (0.95 - 1.81)	1.26 (0.91 - 1.76)

**) Adjusted for* use of nicotine substitutes, malnutrition, kidney failure, COPD, alcohol abuse and antidepressant use.

CI: 95% confidence interval

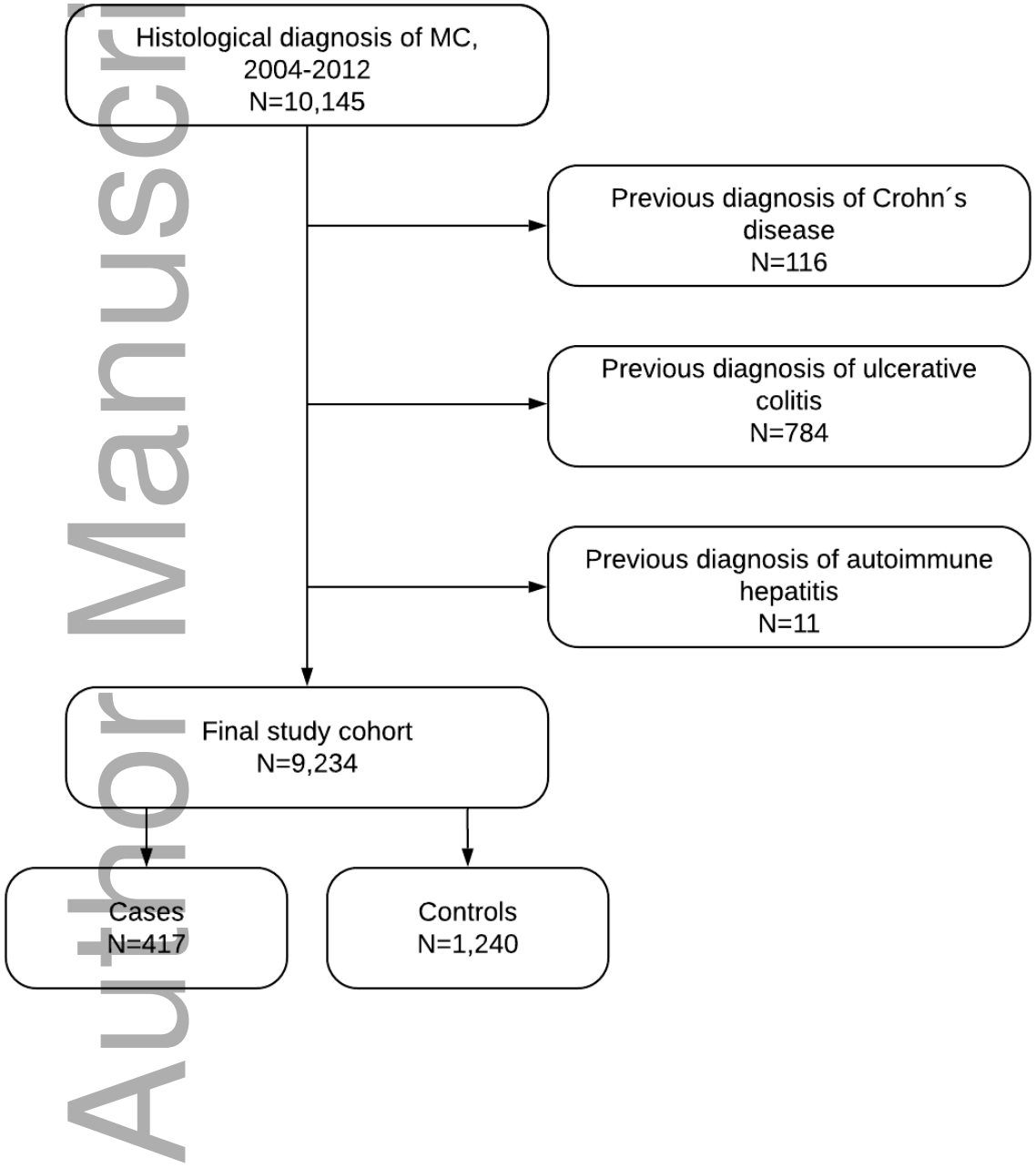
DDD: Defined daily dose

Ref: Reference value

Log: base 2 logarithm

Figures

Figure 1. Identification of the study cohort.



Author contributions

Funding

The study is supported by an unrestricted grant from Tillotts.

Conflicts of interest

Ole Bonderup has received speaker fees from Tillotts and Dr Falk Pharma, is a member of an advisory board for Tillotts and has received grants from Tillotts.

The study is supported by an unrestricted grant from Tillotts.

Jesper Hallas, Martin Thomsen Ernst, Gunnar Lauge Nielsen, and Mette Reilev declare no further conflicts of interest in relation to this study.